Topical Review

Dendritic potassium channels in hippocampal pyramidal neurons

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Potassium channels located in the dendrites of hippocampal CA1 pyramidal neurons control the shape and amplitude of back-propagating action potentials, the amplitude of excitatory postsynaptic potentials and dendritic excitability. Non-uniform gradients in the distribution of potassium channels in the dendrites make the dendritic electrical properties markedly different from those found in the soma. For example, the influence of a fast, calcium-dependent potassium current on action potential repolarization is progressively reduced in the first 150 μm of the apical dendrites, so that action potentials recorded farther than 200 μm from the soma have no fast after-hyperpolarization and are wider than those in the soma. The peak amplitude of back-propagating action potentials is also progressively reduced in the dendrites because of the increasing density of a transient potassium channel with distance from the soma. The activation of this channel can be reduced by the activity of a number of protein kinases as well as by prior depolarization. The depolarization from excitatory postsynaptic potentials (EPSPs) can inactivate these A-type K^+ channels and thus lead to an increase in the amplitude of dendritic action potentials, provided the EPSP and the action potentials occur within the appropriate time window. This time window could be in the order of 15 ms and may play a role in long-term potentiation induced by pairing EPSPs and back-propagating action potentials.

The dendrites of hippocampal pyramidal neurons possess a wide variety of voltage-gated ion channels that are expressed throughout the apical and basal dendrites. Some types of channel are uniformly distributed in the dendrites while others are found to have very non-uniform densities (Johnston *et al.* 1996; Magee *et al.* 1998). Non-uniformities in channel distributions make dendritic electrical properties markedly different from those at the soma. For example, TTX-sensitive Na^+ channels have a uniform density from the soma to at least the first 350 μm of the apical dendrites, but their biophysical properties differ between those found in the soma and distal dendrites in several important ways (see Colbert *et al.* 1997; Mickus *et al.* 1999). The total density of Ca^{2+} channels also appears to be uniform for most of the apical dendrites, but the densities of several of the specific types of Ca^{2+} channel vary considerably (Magee & Johnston, 1995). Certain types of voltage-gated K^+ channels have very non-uniform spatial distributions as do certain hyperpolarization-activated channels (Magee, 1998). This review will focus particularly on one type of voltage-gated and one type of Ca^{2+}-activated K^+ channel in the apical dendrites of hippocampal CA1 pyramidal neurons. We will review what is known about the properties and distribution of these two channel types and then present a working hypothesis for how they may be involved in the induction of long-term potentiation (LTP) of synapses in the distal half of the dendritic tree.

Ca^{2+}-dependent K^+ channels

There are several types of hyperpolarizing after-potentials (AHPs) in hippocampal pyramidal neurons. They have been characterized based on their latency from the action potential, their duration and their pharmacological properties, with fast AHPs mediating in part the repolarization of a single action potential and slow AHPs responsible for the hyperpolarization following a train of action potentials (for reviews, see Storm, 1990; Johnston & Wu, 1995; also Andreasen & Lambert, 1995). From the first

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intradendritic, whole-cell recordings in CA1 neurons, there was evidence that the duration of action potentials in the dendrites is greater than that in the soma (cf. Spruston *et al.* 1995). Furthermore, in contrast to the soma, there seems to be little if any AHP recorded in the dendrites following either single action potentials or trains of action potentials. While the use of gluconate in the whole-cell solutions of these early studies may have contributed to the apparent lack of slow AHPs in the dendrites (gluconate blocks certain types of K^+ channels; Velumian *et al.* 1997), the data nevertheless suggested that AHPs might be preferentially located in the soma or proximal dendrites. Indeed, previous work by Sah & Bekkers (1996) had suggested that the slow AHP following a train of action potentials was expressed mainly in the proximal apical dendrites. Because we were particularly interested in the duration of dendritic action potentials, we focused on the distribution of the fast, Ca^{2+}-activated K^+ current, I_C, which results from activation of BK channels. This conductance is responsible for a fast AHP that helps repolarize somatic action potentials in CA1 pyramidal neurons (Lancaster & Adams, 1986; Storm, 1987; Shao *et al.* 1999). Rather than examine the distribution of single channels as had been done for other channel types (Magee & Johnston, 1995; Hoffman *et al.* 1997; Magee, 1998), we chose instead to use a functional assay by measuring the fast AHP and the rate of repolarization of the action potential as it back-propagates into the apical dendrites (Poolos & Johnston, 1999).

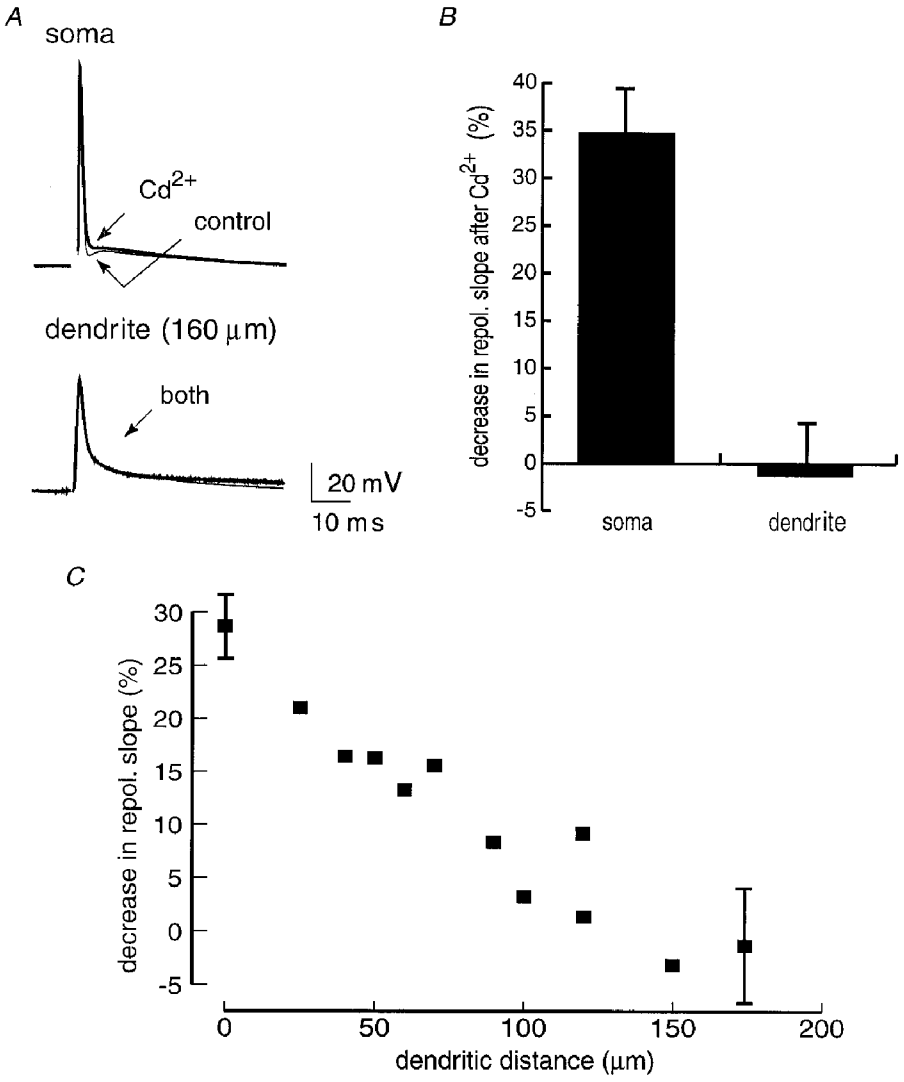

Figure 1. The repolarization of action potentials in the distal dendrites is not affected by Ca^{2+} channel blockade

A, action potentials recorded at the soma (upper traces) are shown under control and 100 μM Cd^{2+} conditions. Superimposed APs show that Ca^{2+} channel blockade significantly slowed AP repolarization and blocked the fast AHP (arrow). Repolarization of dendritic APs (lower traces) was not significantly affected by Ca^{2+} channel blockade. *B*, summary of data showing the average decrease in AP repolarization slope between control and Ca^{2+} channel blockade conditions. *C*, plot of the decrease in action potential repolarization rate with Ca^{2+} channel blockade *versus* distance from the soma (reproduced with permission from Poolos & Johnston, 1999).

The results were quite clear. Using $MeSO_4$ instead of gluconate as the anion in the whole-cell solutions, the fast AHP following an action potential, while present in the soma, was absent in the dendrites (Fig. 1*A*). Furthermore, as had been observed previously, the duration of the dendritic action potential was larger than in the soma and the rate of repolarization was considerably slower. To test for the presence of a fast, Ca^{2+}-activated K^+ current, we measured the rate of repolarization before and after applying the Ca^{2+} channel blocker Cd^{2+}. The rate of repolarization of action potentials in the soma slowed by 35% after applying Cd^{2+}, while action potentials in the dendrites were unaffected by the Cd^{2+} (Fig. 1*B*). These results suggested that there is little if any I_C participating in spike repolarization in the dendrites. This conclusion was further supported by the lack of effect of TEA or charybdotoxin (which are more specific blockers of I_C) on dendritic action potentials (Poolos & Johnston, 1999). We also measured the effect of I_C blockade on spike repolarization as a function of distance from the soma and found that it decreases rather uniformly over the first 150 μm (Fig. 1*C*). From that point to more distal sites there is no effect of Cd^{2+} on spike width, suggesting either that the I_C channels are not present beyond about 150 μm from the soma or that they are not activated by the back-propagating spikes. While in principle the decrease in amplitude of the action potential with distance could contribute to the lack of I_C activation, this seems unlikely to be the only explanation because there is considerable loss of I_C along the first 100 μm of the apical dendrites where the amplitude of the action potential is relatively constant. Therefore, the conclusion drawn from these experiments is that the action potential becomes progressively wider and slower to repolarize as it back-propagates into the dendrites, at least in part because of a lack of I_C. (There may also be differences in delayed rectifier currents between soma and dendrites that contribute to the slowing of the action potential.) The broader dendritic action potential could have important functional consequences for neuronal activity, as will be discussed further below.

Transient K^+ channels

Using cell-attached patch recordings, we found that there is a gradient in the density of transient K^+ channels in the dendrites of CA1 pyramidal neurons (Hoffman *et al.* 1997), increasing 5-fold from the soma to the most distal point measured in the apical dendrites (about 350 μm). (Subsequently, a similar gradient of another channel, I_h, was discovered in the dendrites of these neurons: Magee, 1998, 1999). The transient K^+ channels rapidly activate ($\tau_{act} < 1$ ms) and inactivate ($\tau_{inact} \sim 5$ ms for small depolarizations), and recover from inactivation to about 80% of their initial value in 20–50 ms (see Fig. 2), allowing the channels to open in response to action potentials and EPSPs and thereby influence their amplitude (Cash & Yuste, 1999). Previously, we had found that the density of TTX-sensitive Na^+ channels is approximately the same throughout this same region of apical dendrites (Magee & Johnston, 1995). Taken together, this means that for fast depolarizations the ratio of outward to inward current at any given site in the dendrites increases dramatically with distance from the soma (Fig. 3*A*). This progressively increasing ratio of outward to inward membrane current accounts for the decreasing amplitude of action potentials as they back-propagate into the apical dendrites (Fig. 3*B*). The transient K^+ current in the dendrites is blocked by relatively high concentrations of 4-aminopyridine but is also partially blocked by dendrotoxin (Hoffman *et al.* 1997). These results suggest that the current is due primarily to an A-like conductance, but that a D-like conductance may also be present in the apical dendrites (Storm 1990; Golding *et al.* 1999).

Chemical and electrical modulation of transient K^+ channels

In addition to limiting the amplitudes of back-propagating action potentials, the high density of transient K^+ channels in the dendrites also decreases the amplitude of EPSPs and raises the threshold for dendritic spike initiation (Hoffman *et al.* 1997; Magee *et al.* 1998; Magee & Carruth, 1999). Any

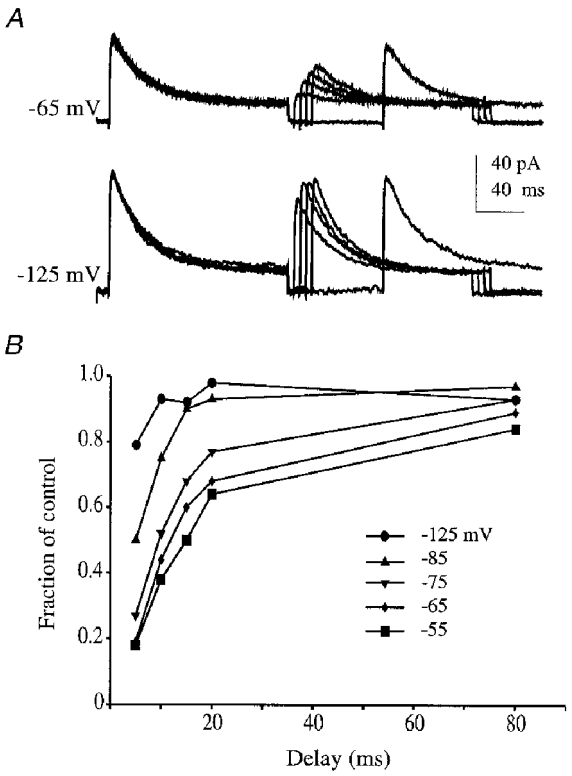

Figure 2. Time course and voltage dependence of recovery from inactivation

A, traces demonstrating recovery from inactivation for two holding potentials, −65 and −125 mV. Long depolarizing steps (150 ms) to +55 mV were given with interpulse intervals of 5, 10, 15, 20 and 80 ms. Recovery is accelerated by holding at hyperpolarized potentials. *B*, summary data. Fraction of total current recovered from inactivation plotted *versus* interpulse interval for each of 5 different holding potentials (from Hoffman, 1999).

change in the activation of these channels could thus have significant consequences for dendritic signal propagation. In recent work, we have found that the transient K^+ current is reduced by a variety of neurotransmitters and second messengers (Hoffman & Johnston, 1998, 1999; see also Colbert & Pan, 1999). For example, activation of protein kinase A, protein kinase C and mitogen-activated protein kinase all reduce this dendritic K^+ current by shifting its voltage range of activation to more positive potentials. The net result of this reduction in the activation of the K^+ current is that the amplitude of the back-propagating action potentials can be increased at distal dendritic locations by the activity of these kinases (Hoffman & Johnston, 1999; Johnston *et al.* 1999). (It is worth noting that all of these kinases have been reported to be involved in various mechanisms for the induction and expression of LTP. For review, see Roberson *et al.* 1996; also Winder *et al.* 1999.) Although not directly tested, such reductions in the K^+

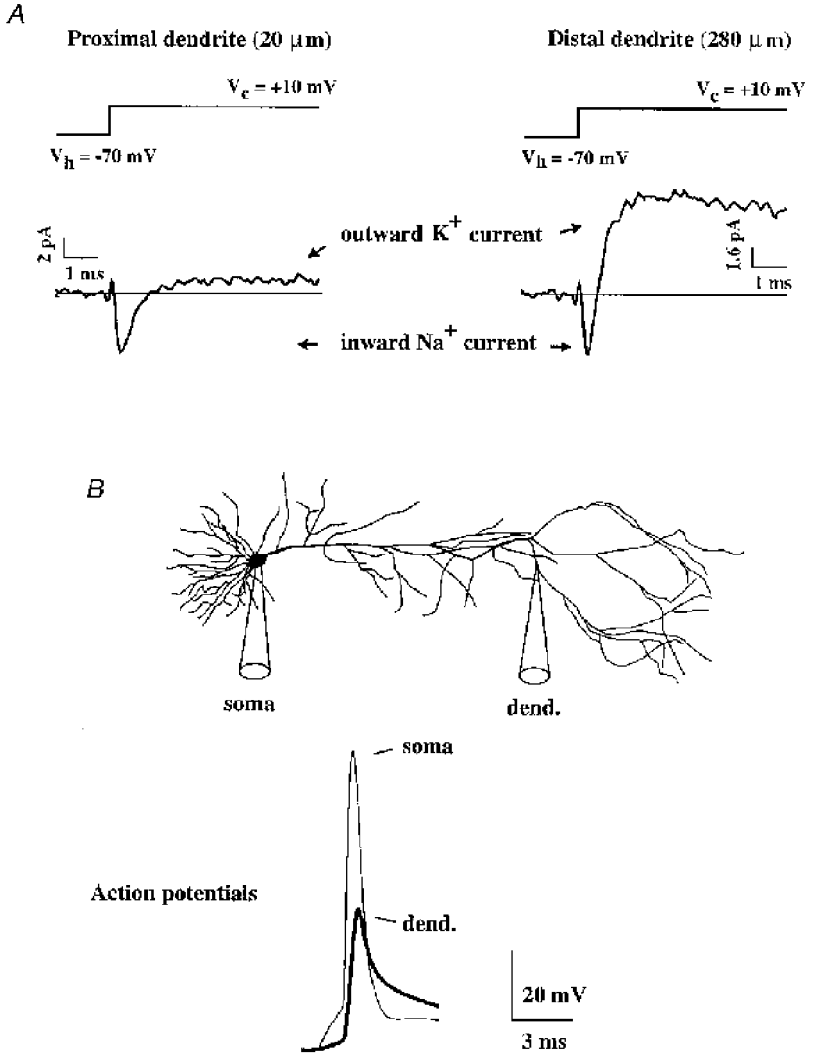

Figure 3. High density of transient K^+ current in dendrites dampens amplitude of back-propagating action potentials

A, the ratio of total voltage-activated inward current to outward current increases from soma to dendrites. Cell-attached patch recordings of composite currents (no channel blockers in patch pipette) are shown that were evoked by an 80 mV voltage step from a holding potential that was near the resting potential (approx. −70 mV). In the trace recorded from the proximal dendrite (left trace), the predominant current is the inward, voltage-gated Na^+ current with the outward K^+ current being of smaller amplitude. In the trace on the right (distal dendrite) the predominant current is the outward, voltage-gated K^+ current with the inward Na^+ current being of relatively smaller amplitude (from Magee *et al.* 1998). *B*, action potentials in dendrites are smaller than in the soma. Dual, whole-cell recordings were made from the soma and from the dendrites (~250 μm from soma) of a CA1 pyramidal neuron as indicated in the diagram at the top. The action potential was triggered by a brief current injection to the soma and back-propagated into the dendrites. The amplitude of the action potential upon reaching the dendrites is smaller because of a high density of K^+ channels and a larger ratio of outward to inward current in the dendrites than in the soma (reproduced with permission from Hoffman *et al.* 1997).

current should also lead to increases in EPSP amplitudes and a general increase in dendritic excitability. Also, because A-type channels rapidly inactivate with depolarization, their effectiveness in controlling dendritic signalling can also be reduced by prior membrane depolarization. In other words, a train of EPSPs can lead to a progressive inactivation of these channels such that subsequent EPSPs and action potentials will be of larger amplitude. This mechanism may play a role during the induction of LTP during repetitive synaptic stimulation, as discussed below.

K^+ current inactivation and LTP induction

If back-propagating action potentials are paired with a brief train of EPSPs, the amplitudes of the action potentials in the dendrites are significantly larger than they would be without the EPSPs (Fig. 4*A*). This increase in dendritic spike amplitude is greater than a simple sum of the EPSP and spike (i.e. there is a supralinear summation) and is due at least in part to K^+ channel inactivation induced by EPSPs. If a number of these paired EPSP spike trains are evoked, LTP is induced (Fig. 4*B*) (Magee & Johnston, 1997). The back-propagation of the action potentials into the dendrites is essential for this form of LTP because local blockade of the spikes near the soma with TTX, which prevents the spikes from invading the distal dendrites, also prevents LTP induction (Fig. 4*C*). These results suggest that at least for some LTP induction protocols (and particularly induction protocols that might occur under physiological conditions in the behaving animals), LTP depends on back-propagating action potentials.

Several groups have explored LTP induction protocols involving the pairing of EPSPs and postsynaptic action potentials (cf. Markram *et al.* 1997; Bi & Poo, 1998; Debanne *et al.* 1998). Using hippocampal CA1 pyramidal neurons, Debanne *et al.* and Bi & Poo demonstrated an interesting timing requirement for synaptic plasticity. If the post-synaptic action potential precedes the EPSP, long-term depression (LTD) is induced. If the postsynaptic action potential follows the EPSP, LTP is induced, but only if the action potential follows within about 20 ms from the onset of the EPSP. Although not explored in those studies, this narrow time window for LTP induction potentially implicates a mechanism involving K^+ channel inactivation. We investigated this hypothesis using a computer simulation of a CA1 pyramidal neuron that included parameters for dendritic Na^+ and K^+ conductances, as described previously (Hoffman *et al.* 1997; Migliore *et al.* 1999). We simulated back-propagating action potentials in the dendrites occurring before and at various times after an EPSP. The results are illustrated in Fig. 5. In the distal dendrites the amplitude of the back-propagating action potential is initially quite small due to the high density of dendritic K^+ channels. However, if the action potential occurs within about 15 ms from the onset of the EPSP, its amplitude is significantly larger due to K^+ channel inactivation. We suggest that if such a mechanism occurred *in vivo*, then the larger action potential could lead to the Mg^{2+} unblocking of NMDA receptors and provide for LTP induction at active synapses. As mentioned above, the action potentials in the dendrites are wider than those in the soma. We suggest that the wider action potential provides a more effective time window for this unblocking of NMDA receptors and the subsequent entry of Ca^{2+}.

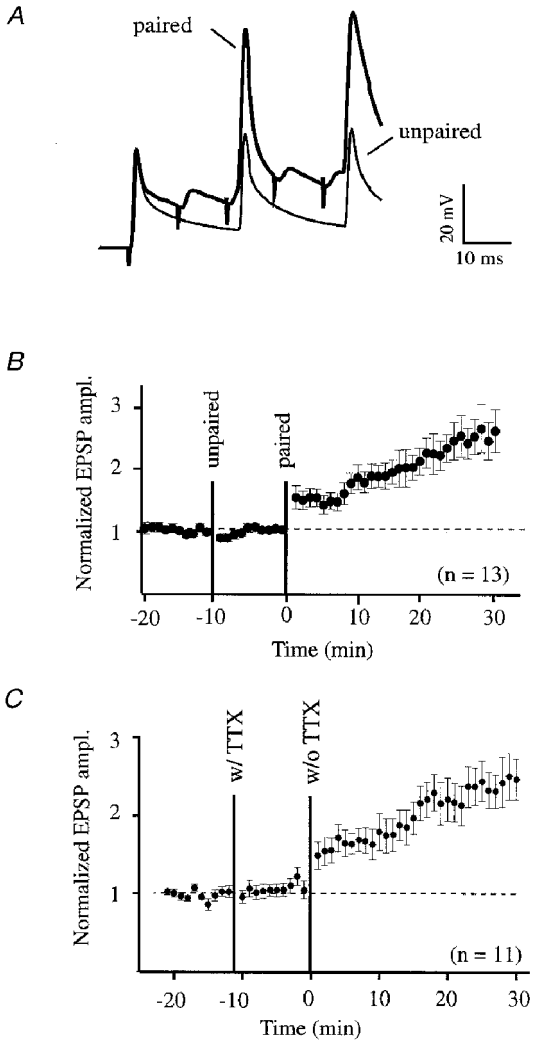

Figure 4. Pairing small EPSPs with back-propagating action potentials induces LTP

A, subthreshold EPSPs paired with back-propagating action potentials increase dendritic action potential amplitude. Actual whole-cell recording at ~240 μm from soma. Action potentials were evoked by 2 ms current injections through a somatic whole-cell electrode at 20 ms intervals. Alone, action potential amplitude was small (unpaired). Paired with EPSPs (5 stimuli at 100 Hz), the action potential amplitude increased greatly (paired). *B*, grouped data showing normalized EPSP amplitude after unpaired and paired stimulation. The pairing protocol shown in *A* was repeated 5 times at 5 Hz at 15 s intervals for a total of 2 times. *C*, a similar pairing protocol was given with and without applying TTX to the proximal apical dendrites to prevent back-propagating action potentials from reaching the synaptic input sites. LTP was induced only when action potentials fully back-propagated into the dendrites (reproduced with permission from Magee & Johnston, 1997).

The ability to control the back-propagation of dendritic action potentials also allows dendritic K^+ channels (primarily the transient A-type) to regulate the action potential firing mode of CA1 pyramidal neurons (single spiking *versus* burst firing). Reduction of distal dendritic K^+ current allows large amplitude dendritic action potentials to effectively activate dendritic Ca^{2+} channels, substantially increasing the duration of dendritic action potentials. The Ca^{2+} current generated by these dendritic spikes propagates to the soma to produce a slow, prolonged membrane depolarization (ADP) that is capable of initiating multiple somatic/axonal action potentials. Modulation of the available dendritic K^+ channel population can, therefore, shift the output state of CA1 neurons from a weakly active single spiking mode to a very active multiple spiking mode (Magee & Carruth, 1999). Such a shift can have important functional consequences. Burst firing has been shown to increase the probability of long-term potentiation (LTP) induction in CA1 pyramidal neurons, suggesting that information storage may be enhanced during this mode of action potential firing (Thomas *et al.* 1998). Furthermore, memory consolidation is hypothesized to occur primarily during the sharp wave or burst firing episodes of slow wave sleep (Buzsaki, 1989).

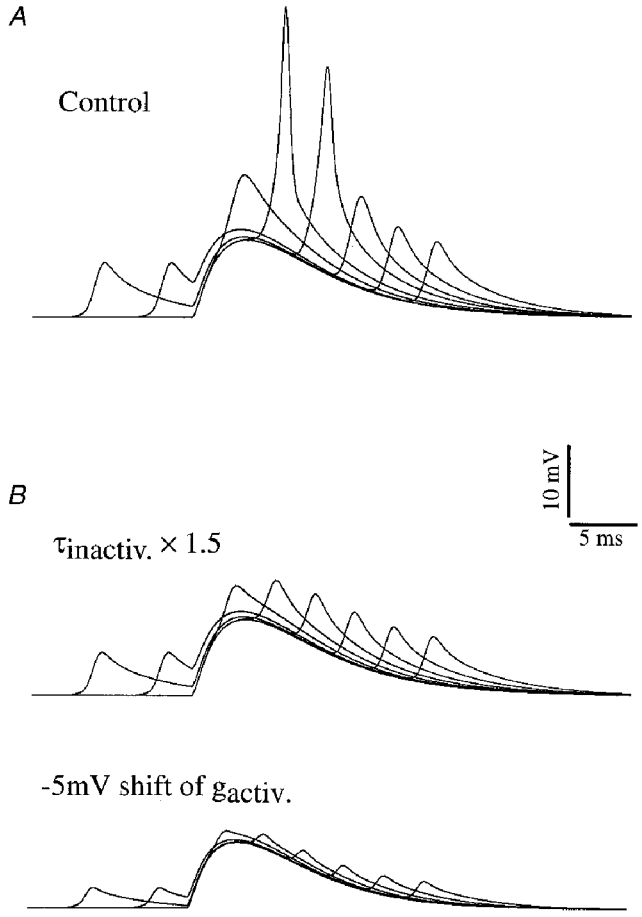

Figure 5. Computer simulation of a distal dendritic site in a CA1 pyramidal neuron in which an EPSP is paired with back-propagating action potentials arriving at different latencies

A, the action potentials arriving within about 15 ms from the beginning of the EPSP are larger due to K^+ channel inactivation. *B*, if the rate of inactivation is slowed by 1·5 times (top) or if the activation curve is shifted by −5 mV (bottom), the increase in action potential amplitude during the EPSP is reduced. Note also that when the voltage range of activation is made more negative (bottom), the amplitude of the action potential is reduced at all latencies because of a larger K^+ current (reproduced with permission from Migliore *et al.* 1999).

Summary

There are many types of voltage-gated ion channels present in the dendrites of hippocampal CA1 pyramidal neurons, some of which exist at remarkably high densities. In this review we have focused primarily on two: the fast, Ca^{2+}-dependent K^+ current, which participates in spike repolarization and elicits a brief after-hyperpolarization following single action potentials, and a transient K^+ current, which rapidly activates and rapidly inactivates with small depolarizations. The lack of a fast Ca^{2+}-dependent K^+ current in distal dendrites is at least one factor responsible for significantly broader dendritic action potentials, which we speculate may provide an effective time window for unblocking NMDA receptors and allowing Ca^{2+} influx during the induction of LTP. The large, transient K^+ current in the dendrites is largely responsible for the declining amplitude of action potentials as they back-propagate into the dendrites as well as for raising threshold for action potential initiation from dendritic depolarizations. While the transient K^+ current can be quite large in the dendrites, it can also be modulated (i.e. reduced) by the activity of a number of protein kinases, including PKA, PKC and MAPK. These kinases in turn are activated by a number of neurotransmitters and second messengers such as noradrenaline (norepinephrine), dopamine, acetylcholine and intracellular Ca^{2+}, all of which are known to operate in this region of the hippocampus.

In addition to chemical modulation, these K^+ channels are also regulated in the neuron by time- and voltage-dependent mechanisms. Depolarization of the cell leads to inactivation of the channels and thereby a reduction in their effectiveness for dampening EPSPs and back-propagating action potentials. Such dynamic regulation of K^+ channels may be an important determinant of whether various activity patterns of pre- and postsynaptic elements lead to strengthening or weakening of synaptic inputs.

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